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Supplementary appendix

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Efficacy, safety, and lot to lot immunogenicity of an inactivated SARS-CoV-2 vaccine (BBV152): a double-blind, randomised, controlled phase 3 trial

Supplementary Appendix 1

Supplementary Appendix 2 - Study Protocol

Supplementary table 1: COVAXIN Study Group and Ethics Committees from all participating trial sites

Hospital Name, City, State (Site Category)	**Ethics Committee Number**	**Principal Investigator**	**Co-Principal Investigator**	**Study Coordinators/Field Worker/Nurse**
Lokmanya Tilak Municipal Medical College and General Hospital, Mumbai, Maharashtra (I)	ECR/175/Inst/MH/2013/RR-19	Nilkanth Awad, MD	1) Siddharth Waghmare, MD 2) Vaibhav Aglawe, MD 3) Jairaj Nair, MD	1) Bhavika Jain 2) Chaitali Babar 3) Poonam Kabale 4) Akash Dhoble 5) Ankur Humare
Grant Government Medical College and Sir J.J Group of Hospitals, Mumbai, Maharashtra (I)	ECR/382/Inst/MH/2013/RR-19	Priti Meshram, MD	1) Dinesh Dhodi, MD 2) Manali Vable, MD 3) Archana Bandkar, MD	1) Mehul Shah 2) Zainab Shaikh 3) Sabir Khan 4) Alex Pandit 5) Smruti Chalke
People's College of Medical Sciences and Research Centre And Associated People's Hospital, Bhopal, Madhya Pradesh (II)	ECR/519/Inst/MP/2014/RR-17	Raghvendra Gumashta, MD	1) Sushil Jindal, MD 2) Chittaranjan Chaubal, MD 3) Sanjay Tandon, MD	1) Saroj Mani 2) Anjlika Jhariya 3) Namrata Manjhi 4) Richa Jain
Nizam's Institute of Medical Sciences, Punjagutta Market, Hyderabad (III)	ECR/303/INST/AP/2013/RR-19	Prabhakar Reddy, MD	1) Ruby Raphael, MD 2) V Bhavani, MD 3) Abid Ali, MD	1) G. Devika 2) Lanka Tejaswi
Gujarat Medical Education and Research Society Medical College and Civil Hospital, Sola, Ahmedabad, Gujarat (II)	ECR/404/Inst/GJ/2013/RR-20	Parul Bhatt, MD	1) Kiran Rami, MD 2) Rashmi Sharma, MD 3) Meera Shah, MD	1) Smruti Parekh 2) Vaishali Chauhan 3) Viraj Salvi 4) Anuj Tarpara 5) Dhaval Kumpavat
Indian Council of Medical Research, National Institute of Cholera and Enteric Diseases, Kolkata, West Bengal (II)	ECR/416/Inst/WB/2013/RR-20	Suman Kanungo, MD	1) Shanta Dutta, MD 2) Agniva Majumdar, MD 3) Jaayanta Saha, MBBS 4) Richa Garg, MD	1) Snehasish Saha 2) Rupesh Mishra 3) Abhijit Guha 4) Dipak Das 5) Arpan Mitra
Institute of Medical Sciences and SUM Hospital, Bhubaneshwar, Odisha (II)	ECR/627/Inst/OR/2014/RR-17	E. Venkata Rao, MD	1) Jyotiranjan Sahoo, MD 2) Smaraki Mohanty, MD 3) Sandeep Kumar Panigrahi, MD	1) Sahazad Ali 2) Banajini Pradhan 3) Manini Sahoo 4) Perween Sultana 5) Binata Samal
All India Institute of Medical Sciences, Patna, Bihar (I)	ECR/1387/INST/BR/2020	Chandramani Singh, MD	1) Sanjay Pandey, MD 2) Pragya Kumar, MD 3) Yogesh Kumar, MD	1) Sarvesh Singh 2) Nitin Kr Singh 3) Achal Singh 4) Shreekant Kumar
Jeevan Rekha Hospital, Belgaum, Karnataka (I)	ECR/1242/INST/KA/2019	Amit Bhate, MD	1) Suresh Bhate, MD 2) Paritosh Desai, MD 3) Abhishek Chavan, MD	1) Ajay Kunal 2) Imran Mulla 3) Sameer Nadaf 4) Laxman Arabhavi 5) Shoiab Shaikh

SRM Medical College and Research Centre, SRM Nagar, Kattankulathur, Tamilnadu (II)	ECR/431/INST/TL/2013/RR-19	Satyajit Mohapatra, MD	1) Melvin George, MD 2) Balaji Ramraj, MD 3) Gayathri Balasubramaniyam, MD	1) Tharunya Palanivel 2) Kalai Selvi 3) Indira Priyadarshini 4) Kamatchi 5) Anusuya
All India Institute of Medical Sciences, Patna, New Delhi (I)	ECR/547/INST/DL/2014/RR-17	Sanjay Rai, MD	1) Randeep Guleria, MD 2) Shashi Kant, MD 3) Praveen Aggarwal, MD	1) Shreya Jha, 2) Suprakash Mandal 3) Tripti Rai 4) Priyanka Bansal 5) Akshay Sharma 6) Kirti Diswar
Prakhar Hospital, Kanpur, Uttar Pradesh (I)	ECR/1017/INST/UP/2017	Jitendra Singh, MD	1) V Tripathi, MD 2) Vikas Mishra, MD 3) Anit Singh, MD	1) Nidhi Singh 2) Astha Singh 3) Saumya Singh 4) Sandeep Uniyal 5) Dev Chaudhary
Rahate Surgical Hospital and ICU, Nagpur, Maharashtra (I)	ECR/601/Inst/MH/2014/RR-17	Manish Multani, MD	1) Prashant Rahate, MS	1) Ashish Tajne 2) Vaishali Tajne 3) Vrushali Mohitkar 4) Pravina Lanjewar 5) Megha Balbudhe
Vydehi Institute of Medical Sciences and Research, Bengaluru, Karnataka (I)	ECR/747/Inst/KA/2015/RR-18	Akshatha Savith, MD	1) Gummadi Reddy, MD 2) Chalapathy DV, MD 3) Natesh Rao, MD	1) Nripesh Nepal 2) Khushboo Sharma 3) Hasina Taj 4) Arun Kumar 5) Payel Sarkar
Mahatma Gandhi Medical College and Research Institute, Pondicherry, Tamil Nadu (II)	ECR/451/Inst/PO/2013/RR-19	Pajanivel Ranganadin, MD	1) Lokesh Shanmugam, MD 2) Vimal Raj, MD	1) Kowshik Reddy 2) Subashri R 3) Soundariya 4) Selva Pandian 5) Agnus Panikar
Redkar Hospital and Research Centre, Pernem, Goa (III)	ECR/902/INST/GA/2018	Sagar Redkar, MD	1) Vivek Redkar, MD 2) Supriya Redkar, MD 3) Shraddha Rane, MD	1) Tejaswini Patil 2) Mrunali Desai 3) Sarvesh Kerkar 4) Jyoti Patil 5) Dhananjay Lad
ESIC Medical College and Hospital, Haryana (II)	ECR/167/Inst/HR/2013/RR-19	Anil Pandey, MD	1) Pooja Goyal, MD 2) Nidhi Anand, MBBS 3) Kranti Garg, MD	1) Bharti Gaur 2) Neha Katiyar 3) Soniya Chahal 4) Ayona James 5) Mohit Prajapati
Directorate of Public Health and Preventive Medicine, Chennai, Tamilnadu (I)	ECR/270/Inst/TN/2013/RR-16	Selvavinayagam Sivaprakasam, MD	1) Palani Sampath, MBBS 2) Sudharshini Subramaniam, MD	1) Savitha Balaji 2) Roshini Azhaguvel 3) Parasuraman Palanivel 4) Sangliraj Muthukalai 5) Ayesha Bee

Sir Ganga Ram Hospital, New Delhi, Delhi (I)	ECR/20/INST/DL/2013/RR-19	Anupam Sachdeva, MD	1) Manas Kalra, MD 2) Pooja Khosla, MD	1) Ajeet Nanda 2) Vinay Sharma 3) Rajni Singh 4) Sakshi Pandey 5) Priyanka Singh
Maharaja Agrasen Hospital, Jaipur, Rajasthan (I)	ECR/745/INST/DL/2015/RR-18	Manish Jain, MD	1) Prabhat Sharma, MD 2) Deepak Sharma, MBBS 3) Madhvender Jain, MD	1) Kapil Soni 2) Khushwant Khatri 3) Sanjeev Vimal 4) Gaurav Dalvi 5) Preshita Vanjare
Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences, Rohtak, Haryana (III)	ECR/293/Inst/HR/2013/RR-19	Savita Verma, MD	1) Dhruva Chaudhary, MD 2) Ramesh Verma, MD 3) Pawan Singh, MD	1) Deepak Gill 2) Anjali Ahlawat 3) Kavita 4) Bijender Singh 5) Rosy
Government Fever Hospital, Gorantla, Guntur (II)	ECR/467/Inst/AP/2013/RR-19	S Laxmi Kumari, MD	1) D Sudheer, MD 2) P Basha, MD	1) Krishna Suri 2) Durga Anjali 3) G Divya 4) K Sowmya 5) K Jyothi
Aligarh Muslim University, Aligarh, Uttar Pradesh (II)	ECR/1418/Inst/UP/2020	Mohammad Shameem, MD	1) Mansoor Tariq, MS	1) Mohammad Shiraz 2) Azimuddin Malik 3) Shafeequr Rahman 4) Nafees Khan 5) Samia Kirmani
Prakash Institute of Medical Science and Research, Islampur, Sangli, Maharashtra (I)	ECR/1052/Inst/MH/2018	Vijaykumar Patil, MD	1) Pradeep Kulkarni, MBBS 4) B Patil, MD	1) Vishwajit Khade 2) Heyeshi Singh 3) Suhash Thorat
Rajashree Chhatrapati Shahu Maharaj Government medical college and Chhatrapati Pramila Raje Hospital, Kolhapur, Maharashtra (I)	ECR/703/Inst/MH/2015/RR-20	Sunita Ramanand, MD	1) Vijay Barge, MD 2) Varun Bafna, MD 3) Rama Bhosale, MD	1) Ratnadeep Patil 2) Shivani Patil 3) Suraj Shewale 4) Sadhana Jadhav 5) Nupur Shevale

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Reverse transcription polymerase chain reaction (RT-PCR)

The ICMR-NIV 2019-nCoV Assay Kit 3.1 contains a set of TaqMan RT-PCR assay for the qualitative detection and characterisation of SARS-CoV-2 RNA. The assay kit uses TaqMan Fluorogenic probe-based chemistry that uses the 5' nuclease activity of Taq DNA polymerase and enables the detection of a specific PCR product as it accumulates during PCR cycles.

The assay includes three targets E gene, ORF 1ab, RdRp of SARS-CoV-2 genes, and one house keeping gene, the β-Actin gene. The assay has one screening and two confirmatory viral genomic region targets, reducing the risk of false negatives.

The assay runs for 40 cycles; however, for any interpretation, the threshold cut off cycle Ct is 35.

Results Interpretation is as follows:

Target	E	ORF	RdRp	β-Actin
Positive	+	+	+/-	+
Negative	-	-	-	+
Strong* Positive (Very low Ct)	+	+	+	-
Sample quality poor	-	-	-	-
Inconclusive	+	-	-	+

The kit was validated by 10 VRDL/Government laboratories who determined that it had 100% specificity and 98·8–100% sensitivity. It passed the WHO External Quality assurance program in 2020 and 2021 with 100% concordance.

Enzyme-linked immunosorbent assay (ELISA) at Screening

The National Institute of Virology (NIV) SARS-CoV-2 Human IgG ELISA kit is intended for qualitative detection of IgG antibodies in serum/plasma of patients presenting clinical signs and symptoms consistent with SARS CoV-2 infection or recovered patients. The sensitivity of the assay is 97·9% percent and specificity 92·3% percent for Laboratory routine testing. Each kit contains one vial of "Positive control" and one vial of "Negative control". These work as markers of kit performance. P/N ratio of Positive control is defined as ratio of OD value of Positive control divided by OD of average OD of Negative control. The test is considered to be valid if P/N ratio is greater than 1.5.

Results are interpreted as follows:

- For an unknown sample (test sample) if O.D. value > Cutoff value and P/N ratio more than 1.5, sample should be considered as "Positive".
- For an unknown sample (test sample) if O.D. value < Cutoff value and P/N ratio less than 1.5, sample should be considered as "Negative".

Enzyme-linked immunosorbent assays (ELISA) done at Bharat Biotech for lot-to-lot comparisons

ELISA tests were performed as per standard protocols. Briefly, microtiter plates were coated with SARS-CoV-2 specific antigens: Whole inactivated SARS CoV-2 antigen; spike (S1) (Syngene, Bangalore, India, Batch No# PRB026913); Receptor Binding Domain (RBD) (Syngene, Bangalore, India, Batch No#PRB025485); nucleocapsid (N) (Syngene, Bangalore, India, Batch No# PRB025627) at a concentration of 1µg/ml, 100µl/well in PBS pH 7·4). After overnight incubation, wells were blocked and serially diluted sera added. After incubation, goat anti-Human IgG HRP conjugate (Sigma-Aldrich, Cat# A8667, dilution 1:5000) was added and incubated for 1 hr at RT. Tetramethyl benzidine was used as a substrate and absorbance measured at 450/630nm. Threshold value (Mean + 3 SD) was established by taking the absorbance of Day 0 sera and antigen-specific endpoint titers were determined for Day 56 sera samples. The reciprocal antibody dilution, at which absorbance is above the threshold, was taken as antigen-specific antibody endpoint titers. All methods were validated with respect to sensitivity and specificity.

Known unvaccinated and uninfected individual sera were used as a negative controls. Simultaneously, ELISA blank (without coating antigen) was also maintained as a negative control. Apart from this, cut off (Mean+3 SD) was drawn from the absorbance obtained at various dilutions (1:1000 to 1:32000) of sera collected on day 0 (before vaccination) which had been found negative in the RT-PCR and serology tests**.**

Using a virus neutralization test as the gold standard, the sensitivity and specificity of the anti-SARS CoV-2 human IgG ELISA was determined to have 93% sensitivity and 100% specificity.

Next-Generation Sequencing

We were able to collect additional Nasopharyngeal swabs (NP) swabs from symptomatic Covid-19 (diagnosed by RT-PCR) participants who provided additional consent. All of the sequences were generated by the ICMR-National Institute of Virology (NIV), Pune, India using a next-generation sequencing approach. Controls were checked to ensure no evidence of amplification in the negative tests and that expected RNA quantification was consistent with cycle threshold (Ct) values provided by the testing laboratories.

All samples were processed by NIV laboratory staffs who were masked to vaccine allocation. In brief, the total RNA was extracted from 200-400 µl of the SARS-CoV-2 real-time RT-PCR positive samples. Extracted RNA was quantified using a Qubit RNA High Sensitivity (HS) kit by Qubit® 2.0 Fluorometer (Invitrogen, Life Technologies). Samples having CT values below 25 were selected for further processing with NGS. A total of 208 primers (104 for Pool#1 and 104 for Pool #2) were designed using the Primal Scheme online tool covering the entire genome of the SARS-CoV-2. A multiplex RT-PCR using the Superscript IV PCR kit (Invitrogen) was performed under the following conditions: 50°C for 30 min; 98°C: 2 min; 35 cycles of 98°C for 10 sec, 56°C for 100 sec, and 72°C for 30 sec and final extension at 72°C for 5 min. The PCR products obtained were loaded (25 µl) onto a 2% Agarose gel and checked for the presence of a PCR product of the desired size.

Bands of around 400 bp were observed in all the Pool 1 and Pool 2 PCR products of samples. Gel extraction of DNA bands was performed using the QIA quick DNA extraction kit protocol. This gel-purified DNA product was used for the library preparation from the A-tailing step by Illumina Truseq LT kit as described earlier (Nyayanit et al, 2020; Yadav et al, 2021). Libraries were quantified using KAPA Library Quantification Kit (Kapa Biosystems, Roche Diagnostics Corporation, USA). Equimolar ratios of libraries were pooled and denatured with 0·1 N NaOH and were neutralised using 0·1 M Tris (pH7·0). The denatured libraries were diluted to 1·3 picomole using hybridization buffers before loading onto Illumina Next seq 550 mid-outputs 300 cycles' reagent cartridges. CLC genomics workbench version11.0 (CLC, QIAGEN, and Germany) was used for the analysis of the data generated from the machine. Reference-based mapping was performed to retrieve the sequence of the SARS-CoV-2.

Nyayanit DA, Sarkale P, Baradkar S, et al. Transcriptome & viral growth analysis of SARS-CoV-2-infected Vero CCL-81 cells. Indian J Med Res 2020; 152: 70–6.

Yadav PD, Potdar VA, Choudhary ML, et al. Full-genome sequences of the first two SARS-CoV-2 viruses from India. Indian J Med Res 2020; 151: 200–9.

Microneutralisation immunogenicity assay method (MNT_{50})

A microneutralisation assay (MNT_{50}) was done at Bharat Biotech for the immunological lot to lot comparisons.

The sera collected from all enrolled participants were inactivated at 56°C in a water bath for 30 min. Sera were successively diluted in a two-fold series from a starting dilution of 1:8 to the required concentration, and an equal volume of challenge virus solution containing 100 $CCID_{50}$ viruses was added. After neutralisation in a 37°C incubator for two hours, a 1.0 x 10^5 /mL cell suspension was added to the wells (0.1 mL/well) and cultured in a CO_2 incubator at 37°C for 3–5 days. The method of Ramakrishnan (2016) was used applied to observations of the cytopathic effect (CPE) to calculate the neutralisation endpoint (MNT_{50}) converting to logarithm the serum dilution that protects 50% of cells from infection by challenge with 100 $CCID_{50}$ virus.

During each assay, a known antibody titre is used as a positive control, and pre-immune sera are used as a negative control.

Ramakrishnan MA. Determination of 50% endpoint titer using a simple formula. World J Virol 2016; 5: 85–6.

Supplementary table 2: Participants' status at baseline for SARS-CoV-2 seropositivity or infection in the three different categories of sites

Site category	Enrolled Participants* (N)	Baseline status			
		IgG positive participants (n)	Seroprevalence (%)	RT-PCR positive participants (n)	Infection rate (%)
I	16,477	5167	31.36%	103	0.63%
II	5313	1775	33.41%	63	1.19%
III	4008	891	22.23%	48	1.20%
Total	**25798**	**7833**	**30.36%**	**214**	**0.83%**

*All enrolled participants who received first dose. No baseline differences were observed across site categories.

Supplementary table 3: Participants disposition status			
Description	**BBV152 (N=12,899) n (%)**	**Placebo (N=12,899) n (%)**	**Total (N=25,798) n (%)**
Screened Participants			26028
Screen Failure			217
Screened but not enrolled			13
Enrolled Participants	12899 (100)	12899 (100)	25798 (100)
Ongoing Participants	12194 (94·5)	12063 (93·5)	24257 (94·.0)
Randomisation Analysis Set [a]	12899 (100)	12899 (100)	25798 (100)
Full Analysis Set (FAS)[b]	8946 (69·4)	8988 (69·7)	17934 (69·5)
Per-protocol Analysis Set (PP)[c]	8471 (65·7)	8502 (65·9)	16973 (65·8)
Immunogenicity Analysis Subset [d]	428 (3.3)	141 (1.1)	569 (2·2)
Safety Analysis Set [e]	12879 (99·8)	12874 (99·8)	25753 (99·8)
Category of Site			
Category 1 (Symptomatic)	8102 (62·8)	8375 (64·9)	16477 (63·9)
Category 2 (Symptomatic/Asymptomatic)	4348 (33·7)	4373 (33·9)	8721 (33·8)
Category 3 (Symptomatic/Asymptomatic + Immunogenicity)	449 (3·5)	151 (1·2)	600 (2·3)
Visit 1 Completed – 1st dose	12,899 (100)	12,899 (100)	25,798 (100)
Visit 2 Completed – 2nd dose	12,310 (95·4)	12,310 (95·4)	24,620 (95·4)
Visit 3 Completed	12,054 (93·5)	12,086 (93·7)	24,140 (93·6)
Visit 4 Completed	11,909 (92·3)	11,893 (92·2)	23,803 (92·3)

(a) All randomised participants classified according to the study product (vaccine or placebo) to which they were randomised.

(b) All randomised participants who received at least one dose of IP and had no immunologic evidence of prior COVID-19 (i.e, negative against SARS-CoV-2 antibodies) at Visit 1 before the first dose of IP. Participants will be analysed according to the study product (vaccine or placebo) received.

(c) All participants in the FAS who received planned doses of IP per schedule, seronegative for SARS-CoV-2 antibody by ELISA at baseline, and had no major protocol deviations, as determined, and documented by the Sponsor.

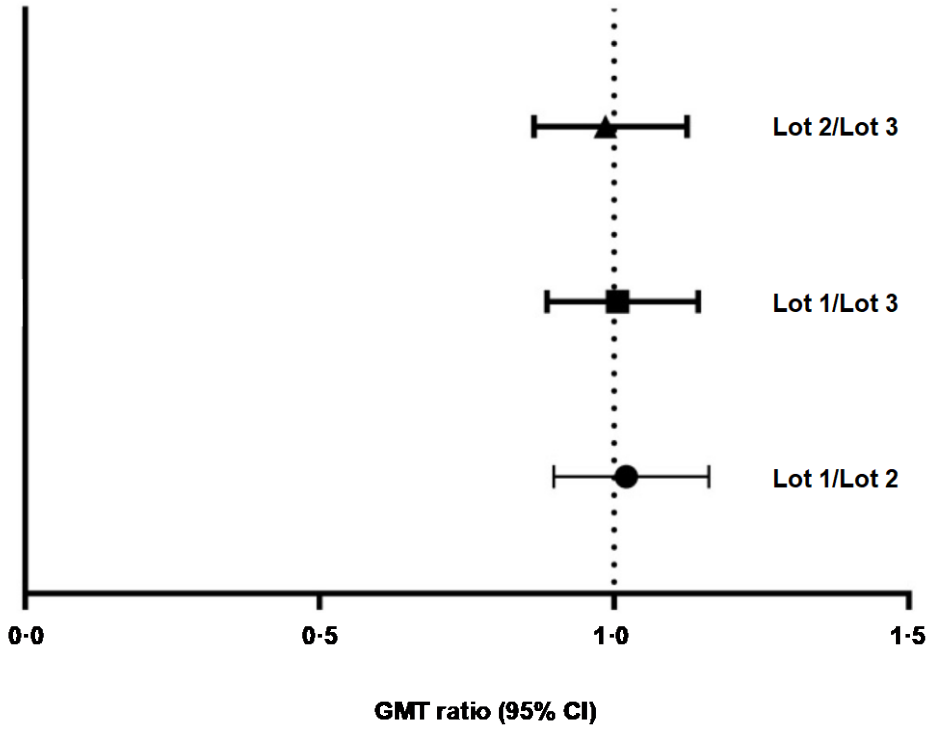
(d) Designated participants at study sites included in the immunogenicity study (category 3) who had received both doses of IP and had no major protocol deviations.

(e) The Safety Set consists of all randomised participants who received at least one dose of IP, classified according to the study product received.

% = n/N *100 where N = number of enrolled participants and n = number of participants.

Database cut-off date: 17 May 2021

Figure 1. Geometric mean ratios of MNT_{50} for three consecutive manufacturing lots of BBV152



Lot-to-lot consistency between treatments was declared if for all lot-to-lot comparisons, the two-sided 95% CI for the GMC ratio was completely contained within 0·5 and 2·0.

Supplementary table 4: MNT_{50} neutralising antibody titres (95% CI) at Day 56 by age and gender					
MNT_{50}		**BBV152 (All lots) (N = 386)**		**Placebo (N = 119)**	
		n	GMT (95% CI)	n	GMT (95% CI)
Age Group (years)	**≥18–<60**	334	129.9 (114.3, 147.6)	101	12.9 (10.1, 16.5)
	≥ 60	52	101.2 (70.0, 146.3)	18	19.1 (9.0, 40.5)
Gender	**Male**	238	118.2 (101.0, 138.3)	77	14.1 (10.4, 19.2)
	Female	148	138.4 (114.4, 167.3)	42	12.9 (8.8,19.0)
SARS-CoV-2 IgG status at baseline	**Negative**	338	118.03 (104.0, 134.0)	99	11.9 (9.3,15.2)
	Positive	48	194.3 (134.4, 280.9)	20	27.4 (14.0, 53.5)

Shown are geometric mean titres measured using the wild-type SARS-CoV-2 microneutralisation assay (MNT_{50}) in sera obtained at Day 56, 4 weeks after the second vaccination.

Supplementary table 5. Summary of adverse events in the Safety Set						
	BBV152 (N = 12,879)		**Placebo** (N = 12,874)		**Total** (N = 25,753)	
	Events n	Participants n (%)	Events n	Participants n (%)	Events n	Participants n (%)
Any Adverse Events	2930	1597 (12·4)	3029	1597 (12·4)	5959	3194 (12·4)
AEs within 7 days of vaccination						
Any AE within 7 days	1949	1223 (9·5)	1720	1136 (8·8)	3669	2359 (9·2)
AE within 7 days post dose 1	1151	809 (6·3)	994	702 (5·5)	2145	1511 (5·9)
AE within 7 days post dose 1	798	568 (4·4)	726	548 (4·3)	1524	1116 (4·3)
Severity of Overall AEs						
Mild	2665	1446 (11.2%)	2680	1394 (10.8%)	5345	2840 (11.0%)
Moderate	181	110 (0.9%)	242	145 (1.1%)	423	255 (0.9%)
Severe	83	40 (0.3%)	102	53 (0.4%)	185	93 (0.3%)
Unsolicited AEs	981	489 (3·8)	1309	609 (4·7)	2290	1098 (4·3)
Serious Adverse Events	40	39 (0·30)	66	60 (0·47)	106	99 (0·38)
All Medically Attended Adverse Events (MAAEs)	475	301 (2·3)	548	319 (2·5)	1023	620 (2·4)
Immediate AEs (within 30 min post vaccination)						
Any immediate AE	14	12 (0·10)	29	23 (0·18)	43	35 (0·14)
Immediate AEs post dose 1	11	10 (0·08)	19	17 (0·13)	30	27 (0·10)
Immediate AEs post dose 2	3	3 (0·02)	10	8 (0·06)	13	11 (0·04)
All Adverse Events of Special Interest (AESI)	23	23 (0·18)	23	23 (0·18)	46	46 (0·18)
All Ongoing AEs	63	41 (0·32)	93	59 (0·46)	156	100 (0·39)

N = number of participants in the relevant population,
Events, n = number of individual events reported (one participant may have reported several AEs),
Participants, n = Number of participants reporting at least one event,
% = n participants with an event/N *100

Supplementary table 6. Incidences of solicited adverse events after each dose.						
Participants reporting solicited AEs within 7 days of vaccination, n (%)	**BBV152** (N = 12,879)		**Placebo** (N = 12,874)		**Total** (N = 25,753)	
	Dose 1 n (%)	Dose 2 n (%)	Dose 1 n (%)	Dose 2 n (%)	Dose 1 n (%)	Dose 2 n (%)
Any Local AE *	431 (3·35)	278 (2·16)	399 (3·10)	260 (2·02)	830 (3·22)	538 (2·09)
Mild	*421 (3·27)*	*272 (2·11)*	*392 (3·05)*	*254 (1·97)*	*813 (3·16)*	*526 (2·04)*
Moderate	*10 (0·08)*	*6 (0·05)*	*7 (0·05)*	*6 (0·05)*	*17 (0.07)*	*12 (0·05)*
Severe	*0*	*0*	*0*	*0*	*0*	*0*
Pain	392 (3·04)	233 (1·81)	358 (2·78)	208 (1·62)	750 (2·91)	441 (1·71)
Erythema	33 (0·26)	21 (0·16)	26 (0·20)	25 (0·19)	59 (0·23)	46 (0·18)
Induration	32 (0·25)	18 (0·14)	26 (0·20)	18 (0·14)	58 (0·23)	36 (0·14)
Swelling	21 (0·16)	14 (0·11)	32 (0·25)	16 (0·12)	53 (0·21)	30 (0·12)
Any Systemic AE *	331 (2·57)	231 (1·79)	247 (1·92)	205 (1·59)	578 (2·24)	436 (1·69)
Mild	*315 (2·45)*	*219 (1·70)*	*231 (1·79)*	*188 (1·46)*	*546 (2·12)*	*407 (1·58)*
Moderate	*15 (0·12)*	*12 (0·09)*	*16 (0·12)*	*17 (0·13)*	*31 (0.12)*	*29 (0·11)*
Severe	*1 (0·01)*	*0*	*0*	*0*	*1 (0·004)*	*0*
Pyrexia	108 (0·84)	86 (0·67)	81 (0·63)	79 (0·61)	189 (0·73)	165 (0·64)
Fatigue	52 (0·40)	41 (0·32)	41 (0·32)	20 (0·16)	93 (0·36)	61 (0·24)
Chills	28 (0·22)	9 (0·07)	22 (0·17)	16 (0·12)	50 (0·19)	25 (0·10)
Headache	128 (0·99)	86 (0·67)	111 (0·86)	70 (0·54)	239 (0·93)	156 (0·61)
Myalgia	49 (0·38)	37 (0·29)	28 (0·22)	28 (0·22)	77 (0·30)	65 (0·25)
Arthralgia	17 (0·13)	12 (0·09)	17 (0·13)	17 (0·13)	34 (0·13)	29 (0·11)
Nausea	17 (0·13)	14 (0·11)	12 (0·09)	10 (0·08)	29 (0·11)	24 (0·09)
Vomiting	12 (0·09)	6 (0·05)	8 (0·06)	8 (0·06)	20 (0·08)	14 (0·05)

N = number of participants in the relevant population,

***** n = number of participants reporting at least one event,

For specific events, n = number of events reported (one participant may have reported several AEs), % = n participants with an event/N*100

No significant differences were observed between the vaccine and placebo groups, with the p values for all comparisons being greater than 0·05.

Supplementary table 7. Serious adverse events (SAE) and deaths by MedDRA system organ class and preferred term at any time during the study, in randomised participants who received at least one dose of vaccine

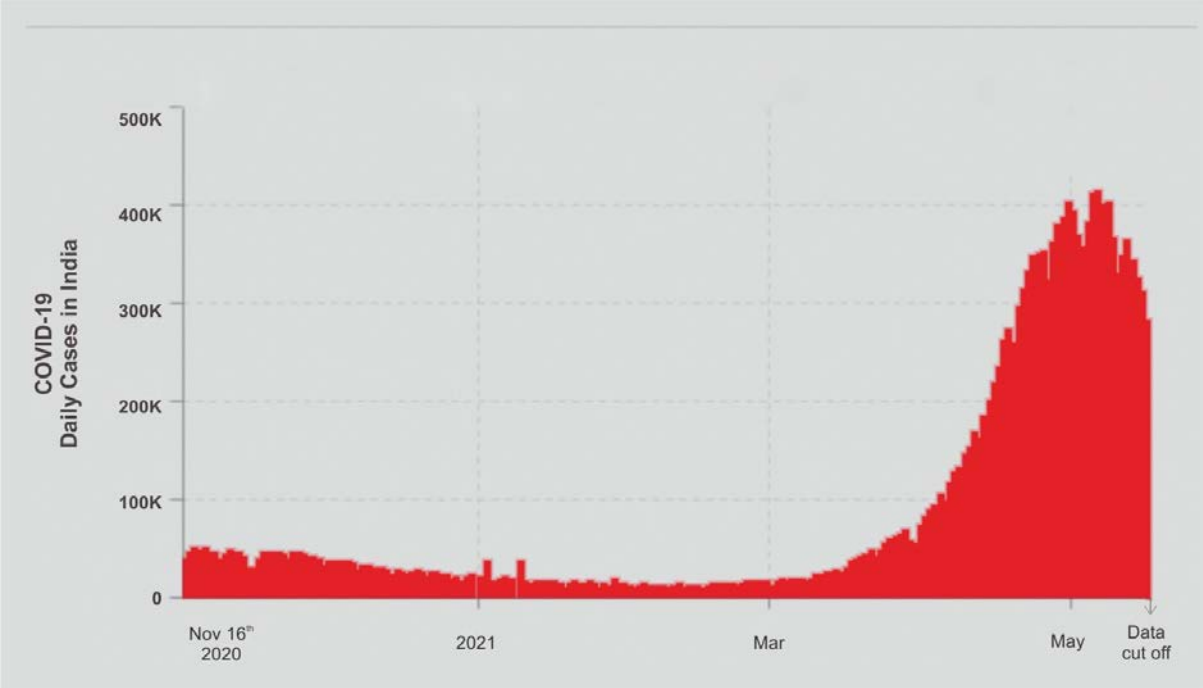
System Organ Class Preferred Term	BBV152 (N = 12,879)			Placebo (N = 12,874)			Total (N = 25,753)		
	m	n	%	m	n	%	m	n	%
Any AEs	40	39	0·303	66	60	0·466	106	99	0·384
Infections and infestations	19	19	0·148	35	35	0·272	54	54	0·210
COVID-19	16	16	0·124	34	34	0·264	50	50	0·194
Otitis media chronic	1	1	0·008	1	1	0·008	2	2	0·008
Hepatic amoebiasis	1	1	0·008	0	0	0	1	1	0·004
Respiratory tract infection	1	1	0·008	0	0	0	1	1	0·004
General disorders and administration site conditions	4	4	0·031	7	7	0·054	11	11	0·043
Death	1	1	0·008	2	2	0.016	3	3	0.012
Pyrexia	2	2	0·016	3	3	0·023	5	5	0·019
Oedema peripheral	0	0	0	1	1	0·008	1	1	0·004
Pain	0	0	0	1	1	0·008	1	1	0·004
Ulcer	1	1	0·008	0	0	0	1	1	0·004
Injury, poisoning and procedural complications	4	4	0·031	2	2	0·016	6	6	0·023
Femur fracture	1	1	0·008	1	1	0·008	2	2	0·008
Foot fracture	0	0	0	1	1	0·008	1	1	0·004
Head injury	1	1	0·008	0	0	0	1	1	0·004
Incisional hernia	1	1	0·008	0	0	0	1	1	0·004
Road traffic accident	1	1	0·008	0	0	0	1	1	0·004
Cardiac disorders	2	2	0·016	5	5	0·039	7	7	0·027
Acute myocardial infarction	1	1	0·008	0	0	0	1	1	0·004
Cardiac arrest	1	1	0·008	1	1	0·008	2	2	0·008
Coronary artery disease	0	0	0	1	1	0·008	1	1	0·004
Left ventricular hypertrophy	0	0	0	1	1	0·008	1	1	0·004
Rheumatic heart disease	0	0	0	1	1	0·008	1	1	0·004
Investigations	2	2	0·016	2	2	0·016	4	4	0·016
SARS-CoV-2 test positive	0	0	0	2	2	0.016	2	2	0·008
Blood homocysteine increased	1	1	0·008	0	0	0	1	1	0·004
Dengue virus test positive	1	1	0·008	0	0	0	1	1	0·004

Gastrointestinal disorders	2	2	0·016	2	2	0·016	4	4	0·016
Duodenal ulcer perforation	1	1	0·008	0	0	0	1	1	0·004
Intestinal Perforation	1	1	0·008	0	0	0	1	1	0·004
Gastritis alcoholic	0	0	0	1	1	0·008	1	1	0·004
Nausea	0	0	0	1	1	0·008	1	1	0·004
Hepatobiliary disorders	1	1	0·008	2	2	0·016	3	3	0·012
Cholecystitis	1	1	0·008	0	0	0	1	1	0·004
Cholelithiasis	0	0	0	1	1	0·008	1	1	0·004
Hepatic cyst	0	0	0	1	1	0·008	1	1	0·004
Eye disorders	0	0	0	2	2	0·016	2	2	0·008
Cataract	0	0	0	2	2	0·016	2	2	0·008
Metabolism and nutrition disorders	1	1	0·008	1	1	0·008	2	2	0·008
Decreased appetite	0	0	0	1	1	0·008	1	1	0·004
Diabetic ketoacidosis	1	1	0·008	0	0	0	1	1	0·004
Nervous system disorders	1	1	0·008	1	1	0·008	2	2	0·008
Haemorrhagic stroke	1	1	0·008	0	0	0	1	1	0·004
Headache	0	0	0	1	1	0·008	1	1	0·004
Renal and urinary disorders	2	1	0·008	1	1	0·008	3	2	0·008
Hydronephrosis	1	1	0·008	0	0	0	1	1	0·004
Nephrolithiasis	0	0	0	1	1	0·008	1	1	0·004
Pelvi-ureteric obstruction	1	1	0·008	0	0	0	1	1	0·004
Respiratory, thoracic and mediastinal disorders	0	0	0	4	2	0·016	4	2	0·008
Chronic obstructive pulmonary disease	0	0	0	1	1	0·008	1	1	0·004
Cough	0	0	0	1	1	0·008	1	1	0·004
Dyspnoea	0	0	0	1	1	0·008	1	1	0·004
Orthopnoea	0	0	0	1	1	0·008	1	1	0·004
Vascular disorders	0	0	0	1	1	0·008	1	1	0·004
Hypertension	0	0	0	1	1	0·008	1	1	0·004
Blood and lymphatic system disorders	1	1	0·008	0	0	0	1	1	0·004
Immune thrombocytopenia	1	1	0·008	0	0	0	1	1	0·004
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	1	0·008	0	0	0	1	1	0·004
Ovarian cancer metastatic	1	1	0·008	0	0	0	1	1	0·004

Pregnancy, puerperium and perinatal conditions	0	0	0	1	1	0·008	1	1	0·004
Abortion incomplete	0	0	0	1	1	0·008	1	1	0·004

N = number of participants in the relevant population
n = Number of participants
m = Count of Events (One participant may be counted more than once)
% = n/N *100.
Serious COVID-19 infections (n=1 and 15 in the vaccine and placebo arms, respectively) met the definition for severe COVID-19 disease as per the protocol/FDA Guidance Document. The remaining serious adverse events related to COVID-19 were hospitalised but symptoms were mild/moderate with no requirement of supplemental oxygen
A total of 15 deaths were reported in the trial with none being related to vaccine or placebo. Three deaths were recorded initially as serious adverse events.

Supplementary Figure 2. Daily cases of COVID-19 in India over the study period during the efficacy analysis.



Data from Johns Hopkins Tracker – Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. Lancet 2020; 20: 533–4.

Supplementary table 8: Variant viral load in symptomatic COVID-19 participants (per protocol set)

All Variants	**Ct values**	**BBV152** Mean	**Placebo** Mean	**Mean ratio BBV152/placebo [95% CI])***
B.1.617.2 (Delta) – E gene	20·11	25·55	18·20	1·42 (1·28–1·57)
B.1.617.2 (Delta) - ORF gene	22·97	28·29	21·09	1·35 (1·24–1·46)
All variants – E gene	20·44	24·01	19·38	1·24 (1·14–1·36)
All variants - ORF gene	23·26	26·55	22·29	1·19 (1·10–1·28)

Data include per-protocol population only. In those participants who met the definition for symptomatic COVID-19 and were PCR-positive an additional nasopharyngeal swab for genotyping was collected. Nasopharyngeal swabs which reported a Cycle Threshold >30 were not subject to genotyping.

*A >1 lower bound for the 95% CI for mean ratio indicates statistical significance; in symptomatic delta variant infections the viral load in the vaccine group was significantly lower than in the placebo group.